TO AF 1656

DM-10/2003

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
Re: Appeal to the Board of Patent Appeals and Interferences

In re Application of: Quirk et al.

Group Art Unit: 1656

Serial No: 10/026,393

Examiner: Sheridan Swope

Filed: December 21, 2001

Our Customer ID: 22827

For: Sensors and Methods for Detection of Proteinase Enzymes

Our Account No: 04-1403

Attorney Ref: KCX-682 (15656)

Sir:

1. [ ] **NOTICE OF APPEAL**: Pursuant to 37 CFR 41.31, Applicant hereby appeals to the Board of Appeals from the decision dated ____ of the Examiner twice/finally rejecting claims ____.
2. [X] **BRIEF** on appeal in this application pursuant to 37 CFR 41.37 is transmitted herewith (1 copy)
3. [ ] An **ORAL HEARING** is respectfully requested under 37 CFR 41.47 (due within two months after Examiner's Answer).
4. [ ] Reply Brief under 37 CFR 41.41(b) is transmitted herewith (1 copy).
5. [ ] "Small entity" verified statement filed: [ ] herewith [ ] previously.
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PATENT

ATTORNEY DOCKET NO: KCX-682 (15656)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF APPEALS AND INTERFERENCES

Appellants: Quirk et al.	)	Examiner: Sheridan Swope
Appl. No: 10/026,393	)	T.C./A.U: 1656
Filed: December 21, 2001	)	Deposit Acct. No: 04-1403
Title: Sensors and Methods for Detection of Proteinase Enzymes	)	Confirmation No: 1033
	)	Customer No: 22827

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U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

BRIEF ON APPEAL

Honorable Commissioner:

Appellants submit the following brief on appeal in accordance with 37 C.F.R. § 41.37:

1. REAL PARTY IN INTEREST

The real party in interest in this matter is the assignee of record, Kimberly-Clark Worldwide, Inc.

2. RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences known to the Appellants or the Appellants' legal representative which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

3. STATUS OF CLAIMS

Claims 82-96 are pending in this application, including independent claim 82. All the claims involved in this Appeal are attached hereto at the Claims Appendix.

Claims 82-96 stand rejected. The rejection of claims 82-96 is hereby appealed.

4. STATUS OF AMENDMENTS

To the Appellants' knowledge, all amendments have been entered into the record.

5. SUMMARY OF CLAIMED SUBJECT MATTER

The captioned application is directed to, in one embodiment, a method for simultaneously detecting the presence of at least two different metalloproteinases in a chronic wound of a human or animal (p. 7, ll. 3-5, Figs. 1C, 3A, and 3B). Independent claim 82, for example, includes collecting a sample of fluid from a chronic wound of a human or an animal (p. 10, ll. 28-29). The sample is then exposed to a plurality of target antibodies (p. 10, ll. 29-32). More specifically, a first target antibody is configured to bind with a first metalloproteinase to form a first target antibody/metalloproteinase complex (p. 3, ll. 30-32), and a second target antibody is configured to bind with a second metalloproteinase to form a second target antibody/metalloproteinase complex (p. 10, ll. 35-38). The first metalloproteinase can be identified by determining the presence or absence of a detectable or measurable manifestation of a first signal element bound to the first target antibody. In addition, the second metalloproteinase can be simultaneously identified by determining the presence or absence of a detectable or measurable manifestation of a second signal element bound to the second target antibody (p. 11, ll. 2-18).

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

In the Final Office Action, claims 82-96 were rejected under 35 U.S.C. §103(a) as being unpatentable over Sorsa, et al. (U.S. Patent No. 5,736,341) in view of Rowe, et al. (Array Biosensor for Simultaneous Identification of Bacterial, Viral, and Protein Analytes, Anal. Chem. **1999**, *71*, 3846-3852) and further in view of Sodek, et al. (Matrix Metalloproteinases in Periodontal Tissue Remodelling, MATRIX Supplement No. 1, pp. 352-362 ©1992).

In the Final Office Action, independent claim 90 was rejected under 35 U.S.C. §112, first paragraph, as not providing enablement for any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claim.

In the Final Office Action, independent claim 90 was rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. Specifically, the claim was rejected as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the Inventors, at the time the application was filed, had possession of the claimed invention.

In addition, claim 90 was rejected under 35 U.S.C. §112, first paragraph for insufficient written description including the introduction of New Matter.

7. ARGUMENT

Appellants respectfully submit that the presently pending claims are patentable over the cited references and that presently pending claim 90 fully complies with 35 U.S.C. §112, first paragraph.

I. Independent claim 82 is patentably distinct over Sorsa, et al. in view of Rowe, et al. and further in view of Sodek, et al.

Sorsa, et al. is directed to a method and test kit for diagnosing periodontal disease. Specifically, antibodies are used to recognize the active form of mammalian MMP-8 and differentiate between the active and proenzyme forms of neutrophil collagenase (MMP-8) (col. 10, ll. 22-32). Sorsa, et al. also describes exemplary test kits for diagnosing periodontal disease (see e.g., cols. 21-22).

Rowe, et al. discloses an array biosensor for simultaneously detecting the presence of different analytes in a sample. The analytes detected by the array biosensor of Rowe, et al. include a bacterial analyte (*Bacillus globigii*), a viral analyte (MS2 bacteriophage) and a proteinaceous analyte (staphylococcal enterotoxin B) presented together in a mixture. The sensor utilizes a standard sandwich immunoassay format in which antigen-specific capture antibodies are immobilized in a patterned array on the surface of a planar waveguide and bound analyte is subsequently detected using fluorescent tracer antibodies. Rowe, et al. describes specific experiments to address the following issues: (1) Can samples be simultaneously tested for the presence of different classes of analytes? (2) Can mixtures of fluorescent tracer antibodies be used effectively? (3) Can the automated software provide quantitative information on the analyte concentration and the level of analyte or antibody cross-reactivity? (4) Can mixtures of analytes in a single sample be measured? (5) Can multiple samples be analyzed simultaneously? (P. 3846, bottom of col. 2 – p. 3847, middle of col. 1.)

Sodek, et al. describes studies of the role certain MMPs play in periodontal disease. Specifically, Sodek, et al. examines the effect of Transforming Growth Factor-β (TGF-β) on polymorphonuclear neutrophilic leucocyte (PMN) derived collagenase,

PMN-derived gelatinase and TIMP (tissue inhibitor of metalloproteinase) (p. 356-358). Sodek, et al. also examines the role of MMP enzymes synthesized by osteoblasts having collagenase and gelatinase activity in alveolar bone remodeling (p. 358 – p. 360).

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Appellant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Moreover, a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). Thus, if certain aspects of a reference are ignored in favor of others, then some motivation must be shown for the person of ordinary skill to follow this preferential selection process.

A. No motivation or suggestion exists to combine Sorsa, et al. and Rowe, et al. as attempted by the Office Action.

As explained by the Federal Circuit, obviousness may only be established by modifying the teachings of the prior art to produce the claimed invention if there is some teaching, suggestion, or motivation to do so found either in the reference itself or in the knowledge generally available to one of ordinary skill in the art. See e.g., In re Fine,

837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988); In re Jones, 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992).

As mentioned above, Sorsa, et al. discloses a method for detecting periodontal disease. The methods include obtaining a GCF sample and contacting the sample with at least one monoclonal antibody that recognizes active mammalian MMP-8 (col. 15, ll. 24-48). The sample can be obtained from a saliva sample, a mouth rinse sample, or a sample of gingival crevicular fluid (GCF) collected with a sampling device (col. 15, ll. 36-59). However, samples are collected preferably in a site-specific manner from GCF associated with a specific site or lesion (col. 11, ll. 45-47).

Sorsa, et al. fails to disclose or suggest limitations of the claims under appeal. For example, and as pointed out in the Final Office Action, Sorsa et al. does not teach a method for detecting a plurality of metalloproteases in a sample. In fact, Sorsa et al. teaches the detection of only one specific MMP in either the active or pro-form, i.e., MMP-8, which is a host derived collagenase (col. 7, ll. 54-67). According to the patent, MMP-8 is "the primary cause of gingival tissue destruction in periodontal disease" (col. 9, ll. 47-53). Moreover, when GCF was examined by Sorsa et al. for detection of a second MMP via Western blot analysis, MMP-1 was not detected. MMP-1 was not detected by specific ELISA recording either. While GCF from periodontitis patients was found to contain increased amounts of MMP-8, hardly any immunoreactive fibroblast-type MMP-1 was found. (Col. 17, ll. 45-60.) Hence, Sorsa et al. teaches that only MMP-8 need be detected in diagnosing periodontitis.

Nevertheless, an attempt was made to combine Sorsa, et al. with Rowe, et al. Rowe, et al. does not include any mention of periodontal disease. None of the analytes

detected by the array biosensor of Rowe, et al. are MMPs. In addition, none of the analytes detected by the array biosensor of Rowe, et al. are related in any way to one another. The reference is specifically directed to testing a sample for simultaneous detection of different classes of analytes, i.e., a virus, a bacterium, and a protein, none of which are related in any fashion to either periodontal disease or matrix metalloproteinases. There is simply no reason why one of ordinary skill in the art, given the teachings of Sorsa, et al. would look to Rowe, et al. for any additional information.

Plainly, the Examiner's only incentive or motivation for attempting to modify Sorsa, et al. using the teachings of Rowe, et al. in the manner suggested in the Office Action results from using Appellants' disclosure as a blueprint to reconstruct the claimed invention out of isolated teachings in the prior art, which is improper under 35 U.S.C. § 103. Appellants note that it is improper to use a patent applicant's own specification to provide the only suggestion for modifying the prior art. The Federal Circuit has repeatedly warned against using the Applicant's disclosure as a blueprint to reconstruct the claimed invention out of isolated teachings in the prior art. See, e.g., Grain Processing Corp. v. American Maize-Products, 5 U.S.P.Q.2d 1788 (Fed. Cir. 1988).

Accordingly, it is respectfully submitted that no proper motivation exists to combine the teachings of Sorsa, et al. with those of Rowe, et al. and any such modification of the cited references relies on the impermissible use of hindsight, which cannot be successfully used to support a *prima facie* case of obviousness.

B. No motivation or suggestion exists to combine Sorsa, et al. and Rowe, et al. with Sodek, et al. as attempted by the Office Action.

In the Final Office Action, and repeated in the Advisory Action, it was stated that Sodek, et al. provides motivation to combine Sorsa, et al. with Rowe, et al. Appellants respectfully submit that Sodek, et al. fails to provide the requisite teaching, suggestion or motivation to combine the references as suggested.

Sodek, et al., as mentioned above, examines the role of certain biochemical factors during the course of periodontal disease. Specifically, Sodek, et al. examines the relationship between TGF-β and collagenase derived from PMNs, gelatinase derived from PMNs, and TIMP. Sodek, et al. also examines the role of MMP enzymes synthesized by osteoblasts having collagenase and gelatinase activity in alveolar bone remodeling.

Sodek, et al. has no more in common with Rowe, et al. than does Sorsa, et al. Sodek, et al. does not mention any of the analytes examined by Rowe, et al., is not interested in any of the issues examined by Rowe, et al. and does not suggest utilization of an array biosensor as is utilized by Rowe, et al. There is simply no reason for someone of ordinary skill in the art, given the teachings of Sodek, et al. to look to Rowe, et al. for any guidance, teaching, or information.

Moreover, even should there be a reason for combining Rowe, et al. with either or both of the other references, there is still no proper motivation to modify Sorsa, et al. as suggested in the Final Office Action, so as to arrive at the claims under appeal.

Sorsa, et al. teaches that the predominant source of host-derived enzymes in gingival tissue, GCF, and salivary collagenases are PMN present in periodontal

inflammation (col. 6, ll. 53-56). In fact, Sorsa, et al. is quite clear in teaching that MMP-8 (neutrophil collagenase) from the PMN cells is the key member of the collagenase/MMP-group that is specifically involved in the progression of tissue destruction seen in periodontal disease (col. 7, ll. 9-12). Sorsa, et al. also teaches that false positives caused by enzymes released in conditions other than active periodontal disease are a major problem when using assays for other suggested enzymes, including some proteinases, and that tests that have been developed for general proteinase activity lack specificity (col. 4, ll. 1-26). Sorsa, et al. also teaches that assays for other proteinases can lead to false negatives and false positive results because of the involvement of these other proteinases in the degradation of non-specific synthetic or natural substrates, such as gelatin (col. 4, ll. 51-55).

Taken as a whole, Sorsa, et al. teaches an assay for detection of MMP-8 as this is the key proteinase that can definitively provide accurate information as to whether a subject is suffering from periodontal disease. More than this, however, Sorsa, et al. also teaches that the assay should not look for additional MMPs, as assays that look for other proteinases can lead to false negatives, false positives, and high background activities. Sorsa, et al. specifically mentions that assays for proteinases that are involved in the degradation of gelatin substrates (e.g., gelatinases) can lead to false positive and false negative results. Sorsa, et al. clearly teaches away from assays for enzymes other than MMP-8 that can lead to false positives, false negatives, and high background activity.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Appellant's

disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Moreover, a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). Thus, if certain aspects of a reference are ignored in favor of others, then some motivation must be shown for the person of ordinary skill to follow this preferential selection process.

Neither Rowe, et al. nor Sodek, et al. provide a motivation for ignoring the aspects of Sorsa, et al. that teach a method for detecting periodontal disease through detection of only MMP-8, and the exclusion of other MMPs. Sodek, et al. discusses the roles of several different MMPs in periodontal disease, including PMN collagenase and PMN gelatinase. Sorsa, et al. also acknowledges that there may be multiple MMPs involved in human periodontal tissue destruction (col. 5, l. 60 – col. 6, l. 13). However, the focus of Sorsa, et al. is that accurate detection of periodontal disease will only be assured through assay for MMP-8, i.e., PMN collagenase. Sorsa, et al. specifically teaches against an assay for gelatinases, which would include PMN gelatinase as is examined in Sodek, et al., as assays for proteinases that degrade gelatin lead to false negatives and false positives (col. 4, ll. 51-55). Sodek, et al. does nothing to contradict the teaching of Sorsa, et al. with regard to accurate detection of periodontal disease. In fact, Sodek, et al. bolsters the basic thesis of Sorsa, et al. that it is collagenase that is the clear benchmark of periodontal disease, "levels of active collagenase were found to correlate strongly with the loss of tooth attachment....Notably, active collagenase was generally absent from control sites" (p. 354, col. 1, ll. 9-12) and "[a] site-specific analysis

of disease in patients with localized juvenile periodontitis confirmed the relationship between tissue destruction and the occurrence of active collagenase in crevicular fluid," (p. 354, col. 2, ll. 3-6).

There is simply no motivation in any of the references to modify the clear, unambiguous teachings of Sorsa, et al., which is directed to a method for detecting periodontal disease through assay for a single matrix metalloproteinase, and instead create an assay for multiple metalloproteinases. Such a modification contradicts the specific teachings of Sorsa, et al. and no motivation for such a contradiction in teaching of the reference has been put forth.

In fact, it appears that the proposed combination of Sorsa, et al. with Rowe, et al. and Sodek, et al. is improperly based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention. Thus, Appellants respectfully submit that no teaching or suggestion would have existed at the time the present invention was made for one of ordinary skill in the art to combine teachings from both Sorsa, et al. and Rowe, et al. with Sodek, et al. and arrive at the method of claim 82.

C. Even if combined, the combination of Sorsa, et al., Rowe, et al. and Sodek, et al. still fails to teach or suggest all of the limitations of independent claim 82.

The Office Action fails to recognize that Sorsa, et al., Rowe, et al. and Sodek, et al., even if taken in some combination, completely fail to teach, disclose or suggest limitations of independent claim 82. Appellants note that it has been long established that in order to establish *prima facie* obviousness, all of the claimed limitations must be

taught or suggested in the prior art. See, e.g., MPEP § 2143.03, citing *In re Royka,* 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

For example, none of the cited references disclose or suggest the step of "collecting a sample from the fluid of a chronic wound", and then simultaneously identifying at least two different metalloproteinases in such a fluid.

In the Final Office Action, it was stated that Sorsa, et al. teach a method for detecting, in a sample of fluid from a chronic, periodontal wound, the matrix metalloproteinase MMP-8. Appellants respectfully disagree and submit that Sorsa, et al. does not disclose or suggest collecting a sample of fluid from a chronic wound, as is found in the claims of the captioned application.

Chronic wounds are well known in the medical arts. Chronic wounds are produced by trauma or pathologic insult and characteristics of chronic wounds include a loss of skin or underlying tissue (Evidence Appendix, 1). Examples of chronic wounds are provided in the Background section of the captioned application and include open cutaneous wounds, burn wounds, neuropathic ulcers, pressure sores, venous stasis ulcers, and diabetic ulcers. Such a wound is neither disclosed nor suggested by Sorsa, et al.

It is well settled that a patentee can act as his own lexicographer (*In re Paulsen*, 30 F.3d 1475, 1480, 31 USPQ2d 1671, 1674 (Fed. Cir. 1994)), and where an explicit definition is provided by the applicant for a term, that definition will control interpretation of the term as it is used in the claim (*Toro Co. v. White Consolidated Industries Inc.*, 199 F.3d 1295, 1301, 53 USPQ2d 1065, 1069 (Fed. Cir. 1999)). Sorsa, et al. does include the term periodontitis lesion in the patent and also includes a definition of what is

intended by the term periodontitis lesion and that it is synonymous with the term periodontitis pocket. Specifically, according to Sorsa, et al., pockets greater than 4 millimeters are considered as periodontitis pockets or periodontitis lesions (col. 2, ll. 18-20). Sorsa, et al. also remains consistent in this definition through the interchangeable use of the terms 'periodontitis pocket' and 'periodontitis lesion' throughout the patent (see, e.g., col. 2, ll. 18-20, col. 6, ll. 8-12, col. 12, ll. 62-65). Periodontitis pockets (or lesions) are further described in the Sodek, et al. reference as caused by the downgrowth of the attached epithelium into the gingival crevice forming a pocket that provides an environment for pathogenic anaerobes. The downgrowth of the epithelium, while providing continued protection to the underlying periodontal tissues, appears to impair regeneration of the lost tissues and can be the location of episodic bursts of inflammatory activity (Sodek, et al., p. 353, last three lines of first column – second column, l. 11).

Thus, the term 'periodontitis lesion' as defined and utilized by Sorsa, et al. is synonymous with the term 'periodontitis pocket', which, as described by Sodek, et al. is a downgrowth of epithelium that provides continued coverage of underlying tissues.

A chronic wound as is found in the claims under appeal is quite different than a periodontitis pocket (or lesion). A wound is defined as, "an injury or damage, usually restricted to those caused by physical means with disruption of normal continuity of structures," (Evidence Appendix, 3) or, "an injury, especially one in which the skin or other external organic surface is torn, pierced, cut or otherwise broken," (Evidence Appendix, 5). The term 'chronic' is defined as, "persisting over a long period of time," (Evidence Appendix, 2), or, "of long duration; continuing; constant," (Evidence

Appendix, 4). Thus, whether considering the accepted clinical definition of a chronic wound, as mentioned above, or combining the standard definition of "chronic" with that of "wound", a periodontitis lesion, as defined and used by Sorsa, et al., is not synonymous with the term "chronic wound."

A periodontitis pocket or lesion of Sorsa, et al. is a downgrowth of epithelium that is characteristic of periodontal disease. This is not an injury or damage caused by physical means persisting over a long period of time, it is not an injury in which the skin or other external organic surface is torn, pierced, cut or otherwise broken and persisting over a long period of time, and it is not produced by trauma or pathologic insult. A chronic wound is quite distinct from a periodontitis lesion as found in Sorsa, et al., and involves completely different causes, biochemical pathways, treatments, and effects. Sorsa, et al. simply does not disclose or suggest collecting a sample of fluid from a chronic wound, as is required in the claims under appeal.

This omission is not cured by the addition of Rowe, et al. or Sodek, et al. As discussed above, Rowe, et al. has little or nothing in common with the other references. No mention of any type of wound, pocket, lesion, or the like is found in Rowe, et al. Sodek, et al., while discussing periodontal pockets, similar to Sorsa, et al., does not teach, suggest, or otherwise mention collecting a sample of fluid from a chronic wound.

The combined references fail to teach additional limitations of the claims under appeal, as well. For instance, even if taken in some combination, the references fail to teach or suggest a method for simultaneously detecting the presence of at least two different metalloproteinases including the step of exposing a sample of fluid collected from a chronic wound to a plurality of target antibodies, wherein a first target antibody is

configured to bind with a first metalloproteinase to form a first target antibody/metalloproteinase complex, and a second target antibody is configured to bind with a second metalloproteinase to form a second target antibody/metalloproteinase complex, as is required in independent claim 82.

As discussed above, Sorsa, et al. discloses a method for detecting MMP-8, Rowe, et al. discloses a method for simultaneously detecting a virus, a bacterium, and a protein, and Sodek, et al., though disclosing detection of several different MMPs, utilizes detection methods that are described as an enzymography technique of Heussen and Dowdle (1980), which is an SDS-PAGE technique that has been modified for increased sensitivity and speed (page 355, col. 1, ll. 4-8).

Even when considering a rejection under 35 U.S.C. § 103, Appellants note that it has long been established that in order to establish *prima facie* obviousness, all of the claimed limitations must be taught or suggested in the prior art. See, e.g., MPEP §2143.03, citing *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). This requirement has not been met in the present case. For instance, *even if* Sorsa, et al. were to be accepted as teaching a method for detecting a single MMP including formation of a first antibody/metalloproteinase complex, neither Sodek, et al. nor Rowe, et al. disclose, suggest or teach a second antibody/metalloproteinase complex as may be utilized in a method for simultaneously detecting at least two different metalloproteinases in a chronic wound.

Appellants respectfully submit that independent claim 82 patentably defines over the cited references.

II. Claim 90 fully complies with 35 U.S.C. §112, first paragraph.

35 U.S.C. §112, first paragraph recites three independent and distinct requirements for the specification:

1) The enablement requirement - To describe the manner and process of making and using the claimed invention in such full, clear, concise, and exact terms as to enable one skilled in the art to make and use the invention;

2) The written description requirement – To describe the subject matter defined in the claims; and

3) To set forth the best mode contemplated by the inventor of carrying out the invention at the time of filing.

The written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), *cert. denied*, 434 U.S. 1064 (1978); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991).

Claim 90, the subject claim of this particular rejection, is directed to a method for simultaneously detecting the presence of at least two different metalloproteinases in a chronic wound of a human or an animal as described above for independent claim 82 with the additional limitation that the first signal element and the second signal element can be the same.

In the Final Office Action, claim 90 was rejected as failing to comply with both the enablement requirement and the written description requirement of 35 U.S.C. §112, first paragraph.

A. Claim 90 fully satisfies the enablement requirement of 35 U.S.C. §112, first paragraph.

To satisfy the enablement requirement, a patent application must describe how to make and use the invention in "such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains...to make and use the same..." (35 U.S.C. §112, first paragraph). The USPTO carries the initial burden to establish a reasonable basis for questioning the enablement provided for the claimed invention (*In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)).

A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. To support an enablement rejection, it must be shown that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims. The scope of enablement is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation (166 F.3d 1196). The enablement requirement is satisfied if the specification describes any method for making and using the claimed invention that bears a "reasonable correlation" to the entire scope of the claims (In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970)).

In the final Office Action, it was stated that the specification does not reasonably provide enablement for identifying two or more metalloproteases using the same signal element. Specifically, it was stated that a person of ordinary skill in the art would not be able to differentiate between any of the possible metalloproteases in the sample if all metalloproteases are detected using the same signal element unless the metalloproteases are first separated, and neither the specification nor the prior art provide sufficient guidance to enable the skilled artisan to make and use the recited invention.

In the Request for Reconsideration dated August 8, 2006, filed in response to the Final Office Action, specific sections of the application were pointed out, including Figures 1C, 3 and 4; page 7, lines 3-15; and page 10, line 5 through page 11, line 18, which describe representative embodiments of a method such as that found in claim 90.

The Advisory Action of September 1, 2006, acknowledged that the specification teaches that a protease can be detected by exposing a sample to a signal element and at least one target antibody and that the specification also states that such a method can be used to simultaneously detect more than one enzyme. Specifically, the Advisory Action points out that representative embodiments pointed out in the Request for Reconsideration use a capture antibody to separate and localize each target protease into reaction sites, wherein the captured proteases are visualized using a second protease-specific antibody labeled with a signal element. Thus, it would appear that the Advisory Action acknowledges that the specification does in fact teach at least one method for simultaneously detecting the presence of at least two different metalloproteinases in a chronic wound of a human or an animal as is found in claim 90.

The Advisory Action goes on to say that the specification fails to teach, without using a protease-specific capture antibody to separate and localize each target protease into reaction sites, how to detect any specific protease in a mixed sample using target antibodies all labeled with the same signal element.

While the specification may not describe in detail each and every method known in the art at the time of the invention for carrying out the method of claim 90, Appellants maintain that the specification, in combination with what is generally known to one of ordinary skill in the art, fully enables claim 90. Information that was well known to persons of ordinary skill in the art need not be included in the specification, and preferably is omitted (*In re Buchner*, 929 F.2d 660, USPQ2d 1331 (Fed. Cir. 1991)). Appellants respectfully submit that multiple methods for detecting two or enzymes in a mixed sample using target antibodies labeled with the same signal element are either described specifically in the application or within the knowledge of one of ordinary skill in the art at the time of the invention.

For example, within the application itself, at least two different methods are described. A first method is described at p. 7, ll. 3-15. According to this particular method, a sensor can include a plurality of reaction sites for simultaneous detection of more than one proteinase enzyme. Each reaction site can contain a target antibody to only one protease enzyme. During use, the sample flows from the sample reservoir through each reaction site. Thus, in this particular embodiment, and in contrast to the statements of the Advisory Action, no additional capture antibody is necessary to simultaneously detect at least two different metalloproteinases.

A second method for simultaneous detection of at least two different metalloproteinases is described between p. 10, l. 5 and p. 11, l. 18. According to this embodiment, a fluid sample including at least one proteinase enzyme is exposed to a signal element and at least one target antibody that is bindable to a target proteinase enzyme to form a target antibody/target proteinase enzyme complex. The complex is then exposed to a capture antibody bindable to the target proteinase enzyme in the complex to form a conjugate. The capture antibody is attached to the surface of the reaction site and only complexes that are bound to the capture antibody will be retained in the reaction site.

Thus, the specification itself describes at least two different methods for carrying out the invention of claim 90, one of which utilizes a capture antibody, and one of which does not. Additional methods for detecting two different proteases, each labeled with a signal element and a target antibody, wherein the signal element is the same in each case, are either encompassed within the specification itself or were known to those of ordinary skill in the art and thus need not be detailed in the specification. For example, in addition to the methods pointed out above, a capture antibody can specifically bind the target antibody of a target antibody/target proteinase enzyme complex. In yet another embodiment, a capture antibody can specifically bind the signal element of a complex.

The paragraph at p. 8, ll. 6-13 discusses the possibility of coupling the signal element and the target antibody to a particle. Thus, yet another embodiment encompassed by claim 90 and described in the application includes incorporating a particle into one of the target antibody/target proteinase enzyme complexes, as

described at page 8. This embodiment is encompassed in currently pending claim 89, in which the first target antibody is bound directly to a particle and the particle is bound directly to the first signal element.

This embodiment is also encompassed in originally filed claim 20, which depends from originally filed independent claim 18:

18. A method for detecting the presence of at least one protease enzyme in a fluid of a human or animal comprising:
a) providing a sample of the fluid of the human or the animal;
b) exposing the sample to a signal element and at least one target antibody, the at least one target antibody bindable to the at least one proteinase enzyme to form a proteinase enzyme/target antibody complex; and
c) exposing the proteinase enzyme/target antibody complex to form a proteinase enzyme/target antibody complex/capture antibody conjugate, to cause a detectable or measurable manifestation of the signal element, thereby indicating the presence of the at least one proteinase enzyme.

20. The method of claim 18, wherein the at least one target antibody and the signal element are attached to a particle.

Thus, pending claim 89 and originally filed claim 20 clearly encompass yet another embodiment of carrying out the method of claim 90, wherein one target antibody and the signal element are attached to a particle, while another target antibody and the signal element (i.e., the second target antibody of pending claim 82 and a target antibody encompassed in the 'at least one' language of original claim 18) are not attached to a particle. Identification of the two complexes either prior to or following the detectable or measurable manifestation of the signal element would be well within the knowledge of one or ordinary skill in the art at the time of the invention via, for example, visual, physical, chemical or any other type of recognition of the particle. Moreover, this particular embodiment of the invention of claim 90 can be carried out with no separation

of the target proteinase enzymes necessary in order to establish the presence of the different metalloproteinases in the sample.

Appellants respectfully maintain that the specification in combination with what was known to one or ordinary skill in the art at the time of the invention provides enablement for the scope of protection sought in claim 90. For at least this reason, Appellants respectfully request withdrawal of the rejection of claim 90 under 35 U.S.C. §112, first paragraph, for lack of enablement.

B. Claim 90 fully satisfies the written description requirement of 35 U.S.C. §112, first paragraph.

To satisfy the written description requirement, a patent specification must describe an invention in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed subject matter," to ensure, e.g., that the inventor had possession of the claimed subject matter as of the desired priority date. *Lockwood v. American Airlines, Inc.,* 107 F.3d 1565, 41 USPQ2d 1961 (Fed. Cir. 1997); *In re Gostelli,* 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989).

As with the enablement requirement, the USPTO carries the initial burden of establishing why a person skilled in the art would not recognize that the written description provides support for the claims. For instance, in order to establish that the written description requirement has not been met, it may be established that a claim element is neither adequately described in the specification, nor conventional in the art, nor known to one of ordinary skill in the art (66 Fed. Reg. 1099 (January 5, 2001)). Similarly, an application may lack adequate written description if a person of ordinary skill in the art can not immediately envisage the claimed invention given the written description (66 Fed. Reg. 1099 (January 5, 2001)).

In the present case, Appellants submit that the specification provides description of several representative embodiments of methods for simultaneously detecting the presence of at least two different metalloproteinases in a chronic wound of a human or an animal as is found in claim 90 and as pointed out in regard to the enablement requirement. For instance, specific description of at least two different representative embodiments for carrying out the method of claim 90 are described in the specification at p. 7, ll. 3-15 and at p. 10, l. 5 and p. 11, l. 18. The particularity provided in these two sections of the application provides evidence that the Appellants invented and were in possession of the subject matter of claim 90.

In addition, methods encompassing the limitations of claim 90 can also be found in originally filed claims 18-30, including independent claims 18 and 26:

18. A method for detecting the presence of at least one protease enzyme in a fluid of a human or animal comprising:

a) providing a sample of the fluid of the human or the animal;

b) exposing the sample to a signal element and at least one target antibody, the at least one target antibody bindable to the at least one proteinase enzyme to form a proteinase enzyme/target antibody complex; and

c) exposing the proteinase enzyme/target antibody complex to form a proteinase enzyme/target antibody complex/capture antibody conjugate, to cause a detectable or measurable manifestation of the signal element, thereby indicating the presence of the at least one proteinase enzyme.

26. A method for treating chronic wounds in a human or animal comprising:

a) providing a sample of the fluid of the human or the animal;

b) exposing the sample to a signal element and at least one target antibody, the at least one target antibody bindable to the at least one proteinase enzyme to form a proteinase enzyme/target antibody complex; and

c) exposing the proteinase enzyme/target antibody complex to form a proteinase enzyme/target antibody complex/capture antibody conjugate, to cause a detectable or measurable manifestation of the signal element, thereby indicating the presence of the at least one proteinase enzyme.

d) identifying the at least one proteinase enzyme by determining the presence or absence of a detectably or measurable manifestation of the signal element; and

e) selecting a treatment for the wound that is effective for treating the identified proteinase enzyme.

It is clear that the methods of the claims utilize only a single signal element, while encompassing multiple proteinase enzymes and multiple target antibodies.

Appellants respectfully submit that there is no element of claim 90 that is not adequately supported by the written description of the application as filed. Claim 90 contains no element that is neither adequately described in the specification, nor conventional in the art, nor known to one of ordinary skill in the art. No explanation has been put forth as to how or why a person of ordinary skill in the art would not immediately envisage the claimed invention given the written description, and particularly the specific descriptions and figures pointed out in the Request for Reconsideration that specifically describe representative embodiments of methods as encompassed in claim 90.

1. Claim 90 does not introduce New Matter to the Application as filed.

In the Final Office Action, claim 90 was also rejected as failing to comply with the Written Description requirement due to introduction of New Matter. Specifically, the Final Office Action stated that the limitation "wherein the first signal element and the second signal element are the same," of claim 90 introduced New Matter because the specification fails to describe said limitation. In the Advisory Action, it was acknowledged that the specification teaches that a protease can be detected by exposing a sample to "a signal element" and at least one target antibody and that the same paragraph of the specification also states that such a method can be used to simultaneously detect more than one enzyme. However, the Advisory Action did not

specifically state that the New Matter rejection was withdrawn. Appellants respectfully reiterate the discussion above with regard to specific representative embodiments of this concept not only in the description portion of the captioned specification, but also in the claims as originally filed in this application, and request withdrawal of the New Matter rejection.

Appellants respectfully maintain that the content of the specification clearly indicates that the inventors invented and possessed the subject matter of claim 90 as of the filing date of the application and request withdrawal of the rejection of claim 90 under U.S.C. §112, first paragraph, as failing to comply with the written description requirement.

In conclusion, it is respectfully submitted that the claims are patentably distinct over the prior art of record, that claim 90 fully complies with U.S.C. §112, first paragraph, and that the present application is in complete condition for allowance. As such, Appellants respectfully request issuance of the patent.

Respectfully submitted,

DORITY & MANNING,
ATTORNEYS AT LAW, P.A.

4/13/07
Date

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8. CLAIMS APPENDIX

82. A method for simultaneously detecting the presence of at least two different metalloproteinases in a chronic wound of a human or an animal, the method comprising:

a) collecting a sample of fluid from the chronic wound, the sample comprising at least two different metalloproteinases;

b) exposing the sample to a plurality of target antibodies, wherein a first target antibody is configured to bind with a first metalloproteinase to form a first target antibody/metalloproteinase complex, and a second target antibody is configured to bind with a second metalloproteinase to form a second target antibody/metalloproteinase complex; and

c) simultaneously identifying the first metalloproteinase and the second metalloproteinase by determining the presence or absence of a detectable or measurable manifestation of a first signal element bound to the first target antibody and a second signal element bound to the second target antibody.

83. The method of claim 82, wherein the first target antibody is configured to preferentially bind to a proenzyme form of the first metalloproteinase.

84. The method of claim 83, wherein the proenzyme form of the first metalloproteinase is selected from the group consisting of proMMP-1, proMMP-8, and proMMP-9.

85. The method of claim 83, further comprising exposing the sample to a third target antibody, wherein the third target antibody is configured to preferentially bind to an active form of the first metalloproteinase.

86. The method of claim 82, wherein at least one of the first target antibody and the second target antibody is a polyclonal antibody.

87. The method of claim 82, wherein the first target antibody is configured to preferentially bind to the active form of the first metalloproteinase.

88. The method of claim 87, wherein the active form of the first metalloproteinase is selected from the group consisting of MMP-1, MMP-8, and MMP-9.

89. The method of claim 82, wherein the first target antibody is bound directly to a particle and the particle is bound directly to the first signal element.

90. The method of claim 82, wherein the first signal element and the second signal element are the same.

91. The method of claim 82, wherein the first signal element and the second signal element are different.

92. The method of claim 82, wherein the first and second signal elements are each independently selected from the group consisting of colorimetric compounds, radio-active compounds, potentiometric elements, fluorescent compounds, chemo-illuminescent compounds, light diffracting elements, and combinations thereof.

93. The method of claim 82, further comprising exposing the sample to a plurality of capture antibodies, wherein each capture antibody is immobilized within a different reaction site, the manifestation of each signal element being identified at each reaction site.

94. The method of claim 93, wherein the target antibodies and the signal elements are contained in a sample reservoir prior to exposure to the sample.

95. The method of claim 94, wherein the reaction sites are in fluid communication with the sample reservoir.

96. The method of claim 95, wherein a collection area is positioned in fluid communication with the reaction sites.

9. EVIDENCE APPENDIX

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2. Dorland's Medical Dictionary – C chrom(o) - - chrotoplast, 2 pgs., **http://www.mercksource.com/pp/us/cns/cns_hl_dorlands.jspzQzpgzEzzSzppdocszSzuszSzcommonzSzdorlandszSzdorlandzSzdmd-a-b-000zPzhtm**.

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4. The American Heritage Dictionary of the English Language, William Morris, Ed., ©1980, Houghton Mifflin Co., Boston, MA, p. 240.

5. The American Heritage Dictionary of the English Language, William Morris, Ed., ©1980, Houghton Mifflin Co., Boston, MA, p. 1476.

Chronic Wound Healing

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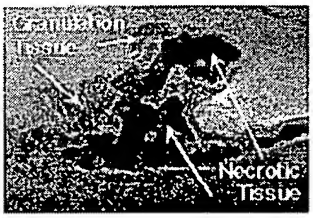
Chronic Wound

Chronic wounds are are a frequently encountered problem in elderly and bedfast patients and are produced by trauma or pathologic insult. Characteristics of chronic wounds include a loss of skin or underlying tissue and do not heal with conventional types of treatment.

The edges of chronic wounds unlike other types of wounds are not approximated and have an accompanying tissue deficit. The professional term for this type of wound is "pressure ulcer" because the cause is often unrelieve pressure over a bony prominance. The general public knows them as either decubiti or "bed sores." What follows is a brief tutorial on various aspects of chronic wound care.



2. Dorlands Medical Dictionary

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C

chrom(o)- - chromoplast

chrom(o)- (chrom(o)-) [Gr. *chrōma* color] a combining form denoting relationship to color.

Chromobacterium (Chro·mo·bac·te·ri·um) (kro"mo-bak-tēr'e-em) [*chromo-* + *bacterium*] a genus of gram-negative, aerobic or facultatively anaerobic, usually nonpathogenic, rod-shaped bacteria, found in soil and water in tropical countries, characteristically producing violet pigment that is soluble in alcohol but not in water or chloroform.

C. viola'ceum a species that may infect humans, causing abscesses, diarrhea, and urinary tract and systemic infections.

chromoblast (chro·mo·blast) (kro'mo-blast) [*chromo-* + *-blast*] an embryonic cell that develops into a pigment cell.

chromoblastomycosis (chro·mo·blas·to·my·co·sis) (kro"mo-blas"to-mi-ko'sis) [*chromo-* + *blasto-* + *mycosis*] a chronic fungal infection of the skin, usually beginning at the site of a puncture wound or other trauma and affecting one lower limb or foot (mossy foot) but sometimes involving other areas of the body, producing wartlike nodules or papillomas that may or may not ulcerate; microscopically, the lesions are characterized by round, brown bodies (sclerotic cells) that reproduce by equatorial splitting and not by budding. It is usually caused by *Phialophora verrucosa*, *Fonsecaea pedrosoi*, *F. compactum*, *Cladosporium carrionii*, or some other dematiaceous fungi. Called also *chromomycosis* and *verrucosa* or *verrucous dermatitis*.

chromocenter (chro·mo·cen·ter) (kro'mo-sen"tar) [*chromo-* + *center* (def. 1)] 1. karyosome. 2. a fused mass of heterochromatin with spokelike extensions of euchromatin, representing portions of the chromosomes in the salivary glands of some insects.

chromocholoscopy (chro·mo·cho·los·co·py) (kro"mo-ko-los'ka-pe) [*chromo-* + *cholo-* + *-scopy*] testing the biliary function by a pigment excretion test (methylthionine chloride).

apparently exert little influence on the phenotypic effect. Called also *accessory* and *B c.*

telocentric c. a chromosome with a terminal centromere; not normally found in humans.

W c.'s the sex chromosomes of certain insects, birds, and fishes, in which the female is heterogametic (i.e., has a W and a Z chromosome) and the males are homogametic (having only Z chromosomes).

X c. the female sex chromosome, being the differential sex chromosome carried by half the male gametes and all female gametes in humans and other male-heterogametic species.

Y c. the male sex chromosome, being the differential sex chromosome carried by half the male gametes and none of the female gametes in man and in some other male-heterogametic species in which the homologue of the X chromosome has been retained.

yeast artificial c. (YAC) a DNA segment, containing up to 1000 kilobase pairs and having a centromere and telomere, introduced into the yeast *Saccharomyces cerevisiae*; it allows the cloning and isolation of much larger DNA segments than is possible using bacterial cloning.

Z c.'s see *W c's*.

chromospermism (chro·mo·sperm·ism) (kro"mo-spər'miz-əm) [*chromo-* + *sperm*] unusual coloration of the sperm.

chromotherapy (chro·mo·ther·a·py) (kro"mo-ther'ə-pe) [*chromo-* + *therapy*] the therapeutic use of light of restricted areas of the spectrum; called also *beam therapy*.

chromotoxic (chro·mo·tox·ic) (kro'mo-tok"sik) [*chromo-* + *toxic*] destructive to hemoglobin or due to the destruction of hemoglobin.

chromotrichia (chro·mo·trich·ia) (kro"mo-trik'e-ə) [*chromo-* + *trich-* + *-ia*] coloration of the hair.

chromotrichial (chro·mo·trich·i·al) (kro"mo-trik'e-əl) pertaining to the coloration of the hair.

chromotropic (chro·mo·trop·ic) (kro"mo-trop'ik) [*chromo-* + *-tropic*] turning to or attracting color or pigment.

chronaxie (chro·nax·ie) (kro'nak-se) chronaxy.

chronaxy (chro·naxy) (kro'nak-se) [*chron-* + Gr. *axios* fit] the minimum time an electric current must flow at a voltage twice the rheobase to cause a muscle to contract.

chronic (chron·ic) (kron'ik) [L. *chronicus*, from Gr. *chronos* time] persisting over a long period of time.

chronicity (chro·nic·i·ty) (kro·nis'i·te) the quality of being chronic.

chron(o)- (chron(o)-) [Gr. *chronos* time] a combining form denoting relationship to time.

chronobiologic (chron·o·bi·o·log·ic) (kron"o-bi"o-loj'ik) pertaining to chronobiology; relating to the effects of time and biologic rhythms on living systems. Written also *chronobiological*.

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W

web - Wytensin

web (web) (web) a tissue or membrane.

antral w. see under *membrane*.

esophageal w. a fibrous, weblike, circumferential fold of the mucous membrane of the esophagus.

laryngeal w. a common congenital malformation of the larynx that may be thin and translucent or thicker and more fibrotic; it is spread between the vocal folds near the anterior commissure and may cause hoarseness, aphonia, and other symptoms. See also *laryngeal atresia*, under *atresia*.

pyloric w. see under *membrane*.

subsynaptic w. a system of filaments or fine canaliculi which have been observed to penetrate at a varying distance into the postsynaptic cell.

terminal w. a feltwork of fine filaments in the cytoplasm immediately beneath the free surface of certain epithelial cells, especially those with a brush border of microvilli, such as the absorptive cells of the intestines and the hair cells of the inner ear; it is thought to have a supportive or cytoskeletal function.

webbed (webbed) (webd) connected by a membrane.

Weber's corpuscle (organ), glands, zone (We'ber's corpuscle (organ), glands, zone) (va'berz) [Moritz Ignatz *Weber*, German anatomist, 1795–1875] see under *gland*, and see *utriculus prostaticus* and *zona orbicularis articulationis coxae*.

Weber's disease (Web'er's disease) (va'berz) [Frederick Parkes *Weber*, English physician, 1863–1962] Sturge-Weber syndrome.

wound (wound) (woond) [L. *vulnus*] an injury or damage, usually restricted to those caused by physical means with disruption of normal continuity of structures. Called also *injury* and *trauma*.

aseptic w. one which is not infected with pathogens.

blowing w. open pneumothorax.

contused w. nonpenetrating w.

incised w. one made by a cutting instrument.

lacerated w. laceration.

nonpenetrating w. one in which there is no disruption of the skin but there is injury to underlying structures. See also *contusion*.

open w. one that communicates with the atmosphere by direct exposure.

penetrating w. one caused by a sharp, usually slender object, such as a nail or ice pick, which passes through the skin into the underlying tissues. Called also *puncture w.*

perforating w. a penetrating wound which extends into a viscus or bodily cavity.

puncture w. penetrating w.

septic w. one that is infected with pathogens.

seton w. one which enters and exits on the same side of the injured part.

subcutaneous w. one which involves only the skin and subcutaneous tissue.

sucking w. a penetrating wound of the chest through which air is drawn in and out. See also *open pneumothorax*.

tangential w. an oblique glancing wound which results in one edge being undercut.

W-plasty (W-plas-ty) (-plas'te) a technique in plastic surgery used mainly in the repair of straight scars that require the redistribution of tension. It consists of excising a series of consecutive small triangular areas of tissue on each side of the wound or scar and imbricating the resultant triangular flaps.

Click here to view image
W-plasty. *(A)*, lines of excision; *(B)*, removal of triangular end flaps and apposition of segments; *(C)*, after suturing.

wrapping (wrapping) (rap'ing) the act or process of putting a cover around a thing.

fundic w. fundoplication.

Wright blood group (Wright blood group) (rit) [*Wright*, surname of the English propositus first reported on in 1953] see under *blood group*.

Wright's stain (Wright's stain) (rits) [James Homer *Wright*, American pathologist, 1869–1928] see *Stains and Staining Methods*, under *stain*.

Late Greek *Khristophoros*, "Christbearer"; from the legend that St. Christopher carried Jesus across a river.]

Chris·to·pher (krĭs'tə-fər), **Saint.** Legendary Christian martyr of the third century A.D.; patron saint of travelers.

Christ's-thorn (krīsts'thôrn') *n.* Any of several plants of the Near East having spiny thorns and popularly believed to have been used for Christ's crown of thorns, such as the jujube or *Paliurus spina-christi*.

chris·ty (krĭs'tē) *n., pl.* **-ties.** A ski turn, the christiania. *(see).*

Chris·ty (krĭs'tē), **Howard Chandler.** 1873–1952. American illustrator, portraitist, and sculptor.

chro·ma (krō'mə) *n.* That aspect of color in the Munsell color system by which a sample appears to differ from a gray of the same lightness or brightness. Chroma corresponds to saturation *(see)* of the perceived color. *See* color. [Greek *khrōma*, color. See ghreu- in Appendix.*]

chro·mate (krō'māt') *n.* A salt or ester of chromic acid. [CHROM(O)- + -ATE.]

chro·mat·ic (krō-măt'ĭk) *adj.* 1. a. Pertaining to colors or color. b. Pertaining to color perceived to have a saturation greater than zero. 2. a. *Music.* Of, pertaining to, or based on the chromatic scale. b. Pertaining to chords or harmonies based on nonharmonic tones. [Greek *khrōmatikos*, from *khrōma*, color, modification of musical tone. See ghreu- in Appendix.*] —**chro·mat'i·cal·ly** *adv.* —**chro·mat'i·cism'** *n.*

chromatic aberration. Color distortion in an image produced by a lens because of the dependence of lens refractivity on the wavelength of light and marked by a variation in the focusing of colors.

chro·ma·tic·i·ty (krō'mə-tĭs'ə-tē) *n.* The aspect of color that includes consideration of its dominant wavelength and purity. See color.

chro·mat·ics (krō-măt'ĭks) *n.* Plural in form, used with a singular verb. The scientific study of color. Also called "chromatology." —**chro'ma·tist** (-mə-tĭst) *n.*

chromatic scale. *Music.* A scale consisting of 12 semitones.

chro·ma·tid (krō'mə-tĭd) *n. Genetics.* Either of two daughter strands of a duplicated chromosome while still joined by a single centromere. [CHROMAT(O)- + -ID.]

chro·ma·tin (krō'mə-tĭn) *n. Genetics.* A complex of nucleic acids and proteins, characterized by intense staining with basic dyes. [CHROMAT(O)- + -IN.]

chromosome
Chromosomes from a lymphocyte of a normal human male

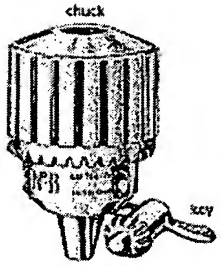
chromato-, chromat-. Indicates: 1. Color, staining, or pigmentation; for example, chromatophore, chromatid. 2. Chromatin; for example, chromatolysis. [From Greek *khrōma* (stem *khrōmat-*), color. See ghreu- in Appendix.*]

chro·mat·o·gram (krō-măt'ə-grăm') *n.* The absorbent column or strip of material containing the stratographically differentiated constituents separated from a solution or mixture by chromatography. [CHROMATO- + -GRAM.]

chro·ma·tog·ra·phy (krō'mə-tŏg'rə-fē) *n.* Separation of complex mixtures by percolation through a selectively adsorbing medium, as through a column of magnesia, gelatin, or starch, yielding stratified, sometimes chromatically distinct, constituent layers. [CHROMATO- + -GRAPHY.] —**chro'ma·tog'ra·pher** *n.* —**chro·mat'o·graph'ic** (krō-măt'ə-grăf'ĭk, krō'mə-tə-) *adj.*

chro·ma·tol·y·sis (krō'mə-tŏl'ə-sĭs) *n. Biology.* The solution and disintegration of stainable material, as of chromatin, within a cell. [CHROMATO- + -LYSIS.]

chro·mat·o·phore (krō-măt'ə-fôr', krō'mə-tə-, -fōr') *n. Biology.* A pigment-containing or pigment-producing cell; especially, a pigment-containing animal cell, as in certain lizards, that by expansion or contraction can change the overall color of the skin. Also called "pigment cell." [CHROMATO- + -PHORE.] —**chro'ma·to·phor'ic** *adj.*



chuck[2]

chrome (krōm) *n.* 1. a. Chromium. b. Anything plated with a chromium alloy. 2. A pigment containing chromium. —*tr.v.* **chromed, chroming, chromes.** 1. To plate with chromium. 2. To tan or dye with a chromium compound. [French, from Greek *khrōma*, color (from the brilliant colors of the chromium compounds). See ghreu- in Appendix.*]

-chrome. Indicates pigment, color, or colored; for example, autochrome. [From Greek *khrōma*, color. See ghreu- in Appendix.*]

chrome alum. A violet-red crystalline compound, $CrK(SO_4)_2 \cdot 12H_2O$, used in tanning, as a mordant, and in photography.

chrome green. 1. Any of a class of green pigments consisting of chrome yellow and iron blue in various proportions. 2. Very dark yellowish green to moderate or strong green. See color.

chrome red. A light orange to red pigment consisting of basic lead chromate with varying proportions of $PbCrO_4$ and PbO.

chrome yellow. Lead chromate, $PbCrO_4$, a yellow pigment often combined with lead sulfate, $PbSO_4$, for lighter hues.

chro·mic (krō'mĭk) *adj.* Of, pertaining to, or containing chromium, especially with valence 3.

chromic acid. 1. A corrosive oxidizing acid, H_2CrO_4, known only in solution. 2. The anhydride of this acid, CrO_3, a purplish crystalline material that reacts explosively with reducing agents and is used in chromium plating, as an oxidizing agent, and to color glass and rubber.

chromic oxide. A bright-green, crystalline powder, Cr_2O_3, used in metallurgy and as a paint pigment.

chromite (krō'mīt') *n.* A widely distributed black to brownish-black chromium ore, $FeCr_2O_4$. [CHROM(O)- + -ITE.]

chro·mi·um (krō'mē-əm) *n. Symbol* **Cr** A lustrous, hard, steel-gray metallic element, resistant to tarnish and corrosion, and found primarily in chromite. It is used as a catalyst, to harden steel alloys, to produce stainless steels, in corrosion-resistant decorative platings, and as pigment in glass. Atomic number 24, atomic weight 51.996, melting point 1,890°C, boiling point 2,482°C, specific gravity 7.10, valences 2, 3, 6. See element. [New Latin, from French *chrome*, CHROM(E).]

chromo-, chrom-. Indicates: 1. Color, colored, staining, or pigment; for example, chromophore, chromosome. 2. Chromium or chromic acid; for example, chromate. [Greek *khrōma*, color. See ghreu- in Appendix.*]

chro·mo·gen (krō'mə-jən) *n.* 1. *Chemistry.* A substance capable of chemical conversion into a pigment or dye. 2. *Biology.* A strongly pigmented or pigment-generating organ or organelle. [CHROMO- + -GEN.] —**chro'mo·gen'ic** *adj.*

chro·mo·lith·o·graph (krō'mō-lĭth'ə-grăf', -grăf') *n.* A colored print produced by chromolithography.

chro·mo·li·thog·ra·phy (krō'mō-lī-thŏg'rə-fē) *n.* The art or process of printing color pictures from a series of stone or zinc plates by lithography. —**chro'mo·li·thog'ra·pher** *n.* —**chro'mo·lith'o·graph'ic** (-lĭth'ə-grăf'ĭk) *adj.*

chro·mo·mere (krō'mə-mĭr') *n.* One of the serially aligned chromatin granules forming a chromosome. [CHROMO- + -MERE.]

chro·mo·ne·ma (krō'mə-nē'mə) *n., pl.* **-mata** (-mə-tə). The coiled filamentous core of a chromosome. [CHROMO- + Greek *nēma*, thread (see snā-¹ in Appendix*).] —**chro'mo·ne'mal** (-nē'məl), **chro'mo·ne·mat'ic** (-mə-nĭ-măt'ĭk), **chro'mo·ne'mic** (-nē'mĭk) *adj.*

chro·mo·phore (krō'mə-fôr', -fōr') *n.* A molecular group capable of selective light absorption resulting in coloration of aromatic compounds. [CHROMO- + -PHORE.] —**chro'mo·phor'ic** (-fôr'ĭk, -fŏr'ĭk) *adj.*

chro·mo·plast (krō'mə-plăst') *n. Botany.* A colored plastid containing a pigment other than or in addition to chlorophyll. [CHROMO- + -PLAST.]

chro·mo·pro·tein (krō'mō-prō'tēn', -prō'tē-ĭn) *n.* A substance consisting of a protein and a chromophore or pigment.

chro·mo·some (krō'mə-sōm') *n.* A DNA-containing linear body of the cell nuclei of plants and animals, responsible for the determination and transmission of hereditary characteristics. [CHROMO- + -SOME (body).] —**chro'mo·so'mal** (-sō'məl), **chro'mo·so'mic** (-sō'mĭk) *adj.* —**chro'mo·so'mal·ly** *adv.*

chro·mo·sphere (krō'mə-sfĭr') *n.* 1. An incandescent, transparent layer of gas, primarily hydrogen, several thousand miles in depth, that lies above and surrounds the photosphere of the sun but is distinctly separate from the corona. 2. A similar gaseous layer around a star. [CHROMO- (from its rosy color) + SPHERE.] —**chro'mo·spher'ic** (-sfĭr'ĭk, -sfĕr'ĭk) *adj.*

chro·mous (krō'məs) *adj.* Of, pertaining to, or containing chromium, especially with valence 2. [From CHROME.]

chron. chronological; chronology.

Chron. Chronicles (Old Testament).

chron·ax·y (krŏn'ăk'sē) *n., pl.* **-ies.** Also **chro·nax·i·a** (-năk'sē'ə), **chro·nax·ie** (-năk'sē). The time interval necessary to stimulate a muscle or nerve fiber electrically with twice the minimum current needed to elicit a threshold response. [French *chronaxie*: CHRONO(S)- + Greek *axia*, value, from *axios*, worthy (see ag- in Appendix*).]

chron·ic (krŏn'ĭk) *adj.* 1. Of long duration; continuing; constant. 2. Prolonged; lingering, as certain diseases. Compare acute. 3. Subject to a disease or habit for a long time; inveterate. [French *chronique*, from Latin *chronicus*, from Greek *khronikos*, pertaining to time, from *khronos*, time.] —**chron'i·cal·ly** *adv.* —**chro·nic'i·ty** (krō-nĭs'ə-tē) *n.*

chron·i·cle (krŏn'ĭ-kəl) *n.* A chronological record of historical events. —*tr.v.* **chronicled, -cling, -cles.** To record in, or in the form of, a chronicle. [Middle English *cronicle*, from Norman French, from Old French *cronique*, from Latin *chronica*, from Greek *(biblia) khronika*, "chronological (books)," from *khronikos*, chronological. See chronic.] —**chron'i·cler** (-klər) *n.*

Chron·i·cles (krŏn'ĭ-kəlz) *pl.n. Abbr.* Chron. In the Old Testament, one of two books, I and II Chronicles.

chrono-, chron-. Indicates time; for example, chronaxy, chronometer. [From Greek *khronos*, time. See chronic.]

chron·o·gram (krŏn'ə-grăm') *n.* 1. The record produced by a chronograph. 2. An inscribed phrase in which certain letters can be read as Roman numerals indicating a specific date. [CHRONO- + -GRAM.] —**chron'o·gram·mat'ic** (-grə-măt'ĭk) *adj.* —**chron'o·gram·mat'i·cal·ly** *adv.*

chron·o·graph (krŏn'ə-grăf', -grăf', krō'nə-) *n.* An instrument that registers or graphically records time intervals such as the duration of an event. [CHRONO- + -GRAPH.] —**chron'o·graph'ic** *adj.* —**chron'o·graph'i·cal·ly** *adv.*

chronol. chronological; chronology.

chron·o·log·i·cal (krŏn'ə-lŏj'ĭ-kəl, krō'nə-) *adj.* Also **chron·o·log·ic** (-lŏj'ĭk). *Abbr.* chron., chronol. 1. Arranged in order of time of occurrence. 2. In accordance with or relating to chronology. —**chron'o·log'i·cal·ly** *adv.*

chronological age. *Abbr.* C.A. The number of years a person has lived, used in psychometrics as a comparison standard for various performance measures. Compare mental age.

chro·nol·o·gy (krə-nŏl'ə-jē) *n., pl.* **-gies.** *Abbr.* chron., chronol. 1. The determination of dates and the sequence of events. 2. The arrangement of events in time. 3. A chronological list or table. [CHRONO- + -LOGY.] —**chro·nol'o·gist** *n.*

chro·nom·e·ter (krə-nŏm'ə-tər) *n.* An exceptionally precise clock, watch, or other timepiece. [CHRONO- + -METER.] —**chron'o·met'ric** (krŏn'ə-mĕt'rĭk, krō'nə-), **chron'o·met'ri·cal** *adj.* —**chron'o·met'ri·cal·ly** *adv.*

chro·nom·e·try (krə-nŏm'ə-trē) *n.* The scientific measurement of time. [CHRONO- + -METRY.]

chron·o·scope (krŏn'ə-skōp', krō'nə-) *n.* An optical instrument

pockets on a jacket. 3. a. Exhausted; spent. b. Showing exhaustion; drawn. 4. Trite; hackneyed. See Synonyms at haggard. [Middle English, past participle of *weren*, to WEAR.]

worn-out (wôrn'out', wōrn'-) *adj.* 1. Worn or used until no longer usable: *a worn-out suit.* 2. Thoroughly exhausted; spent.

wor·ri·ment (wûr'ē-mənt) *n. Informal.* The act or a cause of worrying; worry.

wor·ri·some (wûr'ē-səm) *adj.* 1. Causing worry or anxiety. 2. Tending to worry; anxious. —**wor'ri-some-ly** *adv.*

wor·ry (wûr'ē) *v.* **-ried, -ry·ing, -ries.** —*intr.* 1. To feel uneasy about some uncertain or threatening matter; be troubled. 2. To pull, bite, or tear at something. 3. To work under difficulty or hardship; to struggle: *worried away at a problem.* —*tr.* 1. To cause to feel anxious, distressed, or troubled. 2. To bother; annoy: *Don't worry me with your complaints.* 3. a. To grasp and tug at repeatedly: *a dog worrying a bone.* b. To touch, press, or handle idly; toy with: *worrying the sore tooth with his tongue.* —*n., pl.* **wor·ries.** 1. The act of worrying or the condition of being worried; mental uneasiness or anxiety. 2. A source of nagging concern or uneasiness. —See Synonyms at anxiety. [Middle English *worien, wirien*, to seize by the throat, harass, Old English *wyrgan*, to strangle. See **wer-**[3] in Appendix.*] —**wor'ri-er** *n.*

worry-wart (wûr'ē-wôrt') *n. Informal.* One who tends to worry excessively and needlessly.

worse (wûrs). 1. Comparative of **bad.** 2. Comparative of **ill.** —*adj.* Also *obsolete* **wors·er.** 1. More inferior, as in quality, condition, or effect. 2. More severe or unfavorable. 3. Further from a standard; less desirable or satisfactory. —*n.* Something that is worse. —*adv.* In a worse way. [Middle English *werſe*, Old English *wyrsa*. See **wers-** in Appendix.*]

wors·en (wûr'sən) *v.* **-ened, -en·ing, -ens.** —*intr.* To be or become worse. —*tr.* To make worse.

wor·ship (wûr'shĭp) *n.* 1. The reverent love and allegiance accorded a deity, idol, or sacred object. 2. A set of ceremonies, prayers, or other religious forms by which this love is expressed. 3. Ardent, humble devotion. 4. The object of such devotion. 5. *Often capital* **W.** *Chiefly British.* A title of honor used in addressing magistrates, mayors, and certain other dignitaries. Used with a possessive pronoun: *Your Worship.* —*v.* worshiped or worshipped, **-ship·ing** or **-ship·ping, -ships.** —*tr.* 1. To honor and love as a deity; venerate. 2. To love or pursue devotedly. —*intr.* 1. To participate in religious rites of worship. 2. To perform any act of worship. —See Synonyms at **revere.** [Middle English *worschipe*, Old English *weorthscipe*, honor, dignity, reverence : *weorth*, WORTH + *-scipe*, -SHIP.] —**wor'ship·er** *n.*

wor·ship·ful (wûr'shĭp-fəl) *adj.* 1. Given to or expressive of worship; reverent or adoring. 2. *Chiefly British.* Honorable by virtue of position or rank. Used in titles of respect. —**wor'ship·ful·ly** *adv.* —**wor'ship·ful·ness** *n.*

worst (wûrst). 1. Superlative of **bad.** 2. Superlative of **ill.** —*adj.* 1. Most inferior, as in quality, condition, or effect. 2. Most severe or unfavorable. 3. Furthest from an ideal or standard; least desirable or satisfactory. —**in the worst way.** *Informal.* Very much; a great deal. —*n.* Something that is worst. —**at worst.** Under the worst foreseeable circumstances; if the worst should happen. —**get the worst of it.** To suffer a defeat or disadvantage. —**if (the) worst comes to (the) worst.** At the very worst. —*adv.* In the worst manner or degree. —*tr.v.* **worsted, worsting, worsts.** To gain the advantage over; to defeat. [Middle English *worste, wurst*, Old English *wyrsta*. See **wers-** in Appendix.*]

wor·sted (wo͝os'tĭd, wûr'stĭd) *n.* 1. Firm-textured, compactly twisted woolen yarn made from long-staple fibers. 2. Fabric made from such yarn. —*adj.* Consisting of or made from worsted. [Middle English *worsted*, first made in *Worthestede* (now Worstead), a village in Norfolk, England.]

wort (wûrt, wôrt) *n.* 1. A plant. Used chiefly in combination: *liverwort; milkwort.* 2. An infusion of malt fermented to make beer. [Middle English *wort, wurt*, Old English *wyrt*, plant, herb. See **wərəd-** in Appendix.*]

worth[1] (wûrth) *n.* 1. The quality of something that renders it desirable, useful, or valuable: *the worth of higher education.* 2. The material or market value of something: *have a worth of ten million dollars.* 3. The number or quantity of something that may be purchased for a specific sum: *two dollars' worth of gasoline.* 4. Wealth; riches. 5. The quality within a person that renders him deserving of respect. —*adj.* 1. Equal in value to something specified: *worth its weight in gold.* 2. Deserving of; meriting: *a proposal worth consideration.* 3. Having wealth or riches amounting to: *a man not worth three cents.* —**for all one is worth.** To the utmost of one's powers or ability. [Middle English *worth*, Old English *weorth*. See **wer-**[3] in Appendix.*]

Synonyms: worth, value. These nouns refer to the sum of qualities that make a thing desirable and consequently may determine what it commands in an exchange. They are largely interchangeable when the reference is monetary. Otherwise, *worth* is especially appropriate in denoting qualities in persons or things that add up to moral excellence or to merit considered as an intangible apart from utility. *Value* suggests a more practical, objective scale of measurement. It is most often applied to what is demonstrably useful.

worth[2] (wûrth) *intr.v.* worthed, worthing, worths. *Archaic.* To befall; betide: *"Howl ye, Woe worth the day!"* (Ezekiel 30:2). [Middle English *worthen*, Old English *weorthan*. See **wer-**[3] in Appendix.*]

worth·less (wûrth'lĭs) *adj.* 1. Without worth, use, or value. 2. Without dignity or honor; low and despicable. —**worth'less·ly** *adv.* —**worth'less·ness** *n.*

worth-while (wûrth'hwīl') *adj.* Sufficiently valuable or important to justify the expenditure of time or effort.

wor·thy (wûr'thē) *adj.* **-thi·er, -thi·est.** 1. Having worth, merit, or value; useful or valuable. 2. Honorable; admirable: *a worthy fellow.* 3. Having sufficient worth; deserving: *worthy to be revered; worthy of acclaim.* —*n., pl.* **worthies.** 1. A person esteemed for his worth, dignity, or importance. 2. A figure locally renowned or respected. Often used humorously. —**wor'thi·ly** *adv.* —**wor'thi·ness** *n.*

wost. *Archaic.* Second person singular present tense of **wit** (to know).

wost·teth. *Archaic.* Alternate second person singular present tense of **wit** (to know).

wot. *Archaic.* First and third person singular present tense of **wit** (to know).

Wo·tan (vō'tän). A Teutonic god identified with Woden.

wot·teth. *Archaic.* Alternate third person singular present tense of **wit** (to know).

would. Past tense of **will** (defective verb). See Usage notes at **will, should.**

would-be (wo͝od'bē') *adj.* Desiring or pretending to be.

would-n't (wo͝od'ənt). Contraction of *would not.*

wouldst, would-est. *Archaic.* Second person singular past tense of **will** (defective verb).

wound[1] (wo͞ond) *n.* 1. An injury, especially one in which the skin or other external organic surface is torn, pierced, cut, or otherwise broken. 2. An injury to the feelings. —*v.* **wounded, wounding, wounds.** —*tr.* To inflict a wound or wounds upon. —*intr.* To inflict a wound or wounds. —See Synonyms at injure. [Middle English *wound(e)*, Old English *wund*. See **wā-**[2] in Appendix.*]

wound[2] (wound). 1. Past tense and past participle of **wind** (to wrap). 2. Alternate past tense and past participle of **wind** (to round).

wound-wort (wo͞ond'wûrt', -wôrt') *n.* 1. Any of several plants of the genus *Stachys*, having downy leaves formerly used to treat wounds. 2. Any of several similarly used plants.

wove. Past tense and *rare* past participle of **weave.**

wo·ven. Past participle of **weave.**

wove paper. Paper made on a closely woven wire roller or mold and having a faint mesh pattern. Compare **laid paper.**

wow[1] (wou) *interj.* Used in expressing wonder, amazement, or the like. —*n. Informal.* An outstanding success. —*tr.v.* **wowed, wowing, wows.** *Informal.* To have a strong and usually pleasurable impact on. [Expressive formation.]

wow[2] (wou) *n.* A slow variation in the pitch of sound reproduced by a phonograph or tape recorder, usually the result of irregular movement of a mechanical part. [Imitative.]

WPA Work Projects Administration.

w.p.m. words per minute.

W.r. *Medicine.* Wassermann reaction.

wrack[1] (răk) *n.* 1. Damage or destruction by violent means: *bring to wrack and ruin.* 2. **Wreckage,** especially of a ship cast ashore. 3. A tangled mass of seaweed or other marine vegetation, cast ashore or floating. 4. *British Regional.* Weeds. —*v.* **wracked, wracking, wracks.** —*tr.* To cause the ruin of; wreck. —*intr.* To be wrecked. [Middle English *wrack*, Old English *wræc*, punishment, vengeance, and Middle Dutch *wrak*, wreckage, wrecked ship. See **wreg-** in Appendix.*]

wrack[2]. Variant of **rack** (clouds).

wraith (rāth) *n.* 1. An apparition of a living person. 2. The ghost of a dead person. [Origin unknown.]

Wran·gel Island (räng'gəl). An island, 1,740 square miles in area, off the northeastern coast of Siberia.

Wran·gell, Mount (räng'gəl). An active volcano, 14,005 feet high, at the western end of the Wrangell Mountains.

Wran·gell Mountains (räng'gəl). A range of 100 miles in southeastern Alaska. Highest elevation, 16,420 feet.

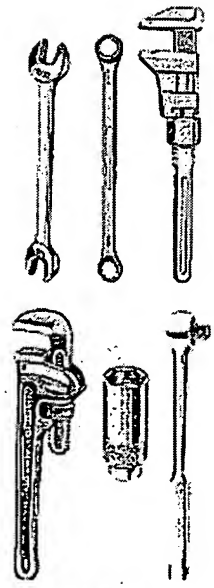
wran·gle (räng'gəl) *v.* **-gled, -gling, -gles.** —*intr.* To dispute noisily or angrily; to quarrel; bicker. —*tr.* 1. To win or obtain by argument. 2. *Western U.S.* To herd (horses or other livestock). —See Synonyms at **argue.** —*n.* 1. An angry, noisy argument or dispute. 2. The act of wrangling. [Middle English *wrangelen*, probably of Low German origin, akin to Low German *wrangeln*. See **wer-**[3] in Appendix.*]

wran·gler (räng'glər) *n.* 1. One who wrangles. 2. A cowboy, especially one who tends saddle horses. 3. A winner of the highest honors in mathematics at Cambridge University.

wrap (răp) *v.* **wrapped** or **wrapt, wrapping, wraps.** —*tr.* 1. To arrange or fold about in order to cover or protect something: *She wrapped her coat about her.* 2. To cover, envelop, pack, or encase. 3. To package, as with paper. 4. To clasp, fold, or coil about something: *She wrapped her arms about his neck.* 5. To envelop and obscure, often with the effect of concealing or disguising the nature of: *Fog wrapped the countryside.* 6. To involve in some condition: *wrapped in grief; wrapped in mystery.* —*intr.* 1. To coil, wind, or twist about or around something: *The flag wrapped around the pole.* 2. To put on warm clothing; bundle up. Used with *up.* —*n.* 1. A garment to be wrapped or folded about a person; especially, a robe, cloak, shawl, or coat. 2. A blanket. 3. A wrapping or wrapper. —**keep under wraps.** To keep secret or concealed. [Middle English *wrappen*, probably from Germanic, akin to Danish dialectal *vravle*, to twist.*]

wrap-a-round (răp'ə-round') *adj.* 1. Designating a garment such as a dress, skirt, or robe, that is open to the feet and that is wrapped around the body before being fastened. 2. Having ends that curve back or that overlap the sides.

wrap·per (răp'ər) *n.* 1. One that wraps. 2. The outer or other



wrench
Above, from left: Open-end wrench; long-box wrench; monkey wrench
Below, from left: Stillson wrench; socket wrench and fixture

10. RELATED PROCEEDINGS APPENDIX

None